Greetings: November 8, 2000

The following constitutes a *personal* statement of dissent with respect to certain conclusions of this risk assessment for malathion.

Given the formidable weight of opinion contrary to my views in our cancer and non-cancer committee reports, two pathology working groups, and evident at the August 2000 SAP convened on the cancer issues, there is probably little I could say here in so brief a time span that would secure any particular change of persuasion. However, *conscience compells my presence here, maintaining the correctness of my evaluations of the data base*.

The concerns I have with respect to this risk assessment, particularly the health effects aspects, are many, involving both cancer and non-cancer toxicology issues. Fortunately, most of my observations and scientific concerns have now been included as attachments to the final reports of the cancer and non-cancer committees, and in the docket of the August SAP meeting for all interested persons to evaluate for themselves. The very fact that these reviews and memoranda have been included represents an accomplishment on the part of OPP and the Agency's professional employee's Union in the area of securing expression of scientific dissent. I must acknowledge that the information may be so extensive as to discourage people from seriously considering it. In any case, it is available on EPA's web site, or in the SAP Docket, and there is really no need for me to attempt to explain it here in any detail.

My concerns might be briefly traced as follows:

I) ***Carcinogenicity Issues***

A) Concerning OPP's Assessment

I Do not find acceptable our cancer committee's interpretations regarding the following:

> Liver tumor responses in the mouse and rat bioassays, nor I might add can I accept either of the respective PWG reports on these liver tumor findings.
>
> Rare nasal cavity tumor findings in the rat, where substantial evidence of nasal tissue vulnerability to malathion is evident, in both the rat and mouse.
>
> Rare squamous cell tumor findings of the palate in the rat, in concert with the absence of full histopathology assessment of the oral cavity.
>
> Thyroid C-cell tumor response in the rat.
>
> Thyroid follicular cell tumor response in the rat.
>
> Testicular interstitial cell tumor response in the rat

Leukemia in the rat

Supporting documentation for these findings, as previously indicated, is a matter of the record.

Given the remarkably high incidences of liver tumors in mice of both sexes at the higher dose levels, I do not concur with the *removal of the quantitative risk assessment for carcinogenicity as being compatible with the Agency's responsibility for the protection of public health.*

I have considerable disagreement with our cancer committee's understanding and use of principles of interpretation of neoplastic findings in cancer bioassays as set forth in various authoritative sources. For example:

> The discounting (without justification) of positive neoplastic findings at doses considered excessive, while accepting negative findings at those same doses, where competing toxicity and increased mortality may preclude or compromise full expression of neoplastic responses.

Using cholinesterase inhibition in the absence of other evidence an MTD has been reached or exceeded, to conclude dosing to be excessive and in effect discounting tumor findings at such doses.

> Discounting the two highest dose groups in a cancer bioassay on the grounds dosing was excessive, *while considering what remains of that study to constitute a satisfactory study,* even though the number of dose groups remaining is inadequate, dose levels are too low and all protocol tissues required for the high dose group are not examined in the lower dose group which in effect must become an acceptable high dose group.

Employing less remarkable tumor findings at high dose levels, considered excessive, to discount significantly positive tumor findings of the same kind in an acceptable lower dose range, which I might add, are of inherently greater concern because of the *enhanced concern over findings in the lower dose range.*

> *Inadequate review of the collective evidence of carcinogenicity at very low doses.* ***{for my information: mouse liver, rat [liver (if "key events" included), nasal (if "key events" included), oral, testicular, thyroid c-cell and leukemia (based on enhanced tumor development)]}***

> Inordinate focus upon statistical treatment of tumor incidence data versus other evidence of carcinogenicity, resident in such findings as enhanced tumor development.

I find a need for an external review of the entire malathion mutagenicity data base.

In my view, the carcinogenicity data base should be evaluated from a *conservative public health perspective,* yet I have doubts this has been a guiding principle of our cancer committee.

B) Concerning the SAP Review

Though I was accorded an opportunity to present my views to the SAP convened last August, I am not satisfied my views received proper attention. The data base is complicated, and there was inadequate time for me to present, *via the spoken word*, any more than a fraction of my documented concerns. However, my *written presentation* was submitted to the SAP in the formal manner via the FIFRA Designated Official one week prior to the meeting. Yet, on the occasion of the SAP meeting, I witnessed no evidence the SAP responded to my written presentation. A case in point is that of the SAP's response to the Agency's formal questions. At the point in time when SAP responded to *the questions*, which is a focal point of the SAP hearing, *it was the Agency's questions that were addressed.* In my written submission there were some 35 questions directed to the SAP, none of which were acknowledged at the SAP meeting. *OPP is clearly in the drivers seat at these meetings.* OPP determines the questions to be responded to by SAP, and OPP did not direct the SAP to the questions posed in my submission, as should be required in an *equitable hearing*. I was forced to trust that SAP Panelists would read my presentation, and insist upon addressing my questions at the meeting. In retrospect, I would have approached it differently and sought before hand a mechanism to secure a level playing field before the SAP. The bottom line is that the SAP hearing was not equitable, and my opportunities were very truncated. For this reason *I am now petitioning OPP* to have the SAP yet respond to my questions, which would in effect involve more critical consideration of my views.

II) ***Non-Cancer Issues***

A) Concerning OPP's Assessment

Deletion of the FQPA imposed 10X safety factor for the protection of infants and children is indefensible, as our committee has *not* been successful in establishing the malathion data base to be: a) *complete*, b) *reliable* and c) *absent evidence of increased susceptibility of the young* versus adult animal, as required under FQPA. For example, I maintain the evidence of increased pup sensitivity in the malathion reproduction study, a focal study for assessing susceptibility of the young, cannot be discounted on the basis of the committee's argument of increased consumption of malathion via dam's milk, *absent identification of malathion in the milk*, let alone any quantitative assessment of the same. I further maintain other studies presented to the same committee, particularly a published work showing a *nine-fold* greater sensitivity of neonatal versus weanling rats resulting from acute administration of malathion, serve to illustrate enhanced susceptibility of the young to this organophosphate.

Existing evidence does not support the conclusion that a single dose of malathion as high as 50 mg/kg would be without toxicological consequences in either the maternal or the developing organism, and should not serve as the basis for the committee's selection of the acute (one-day) RfD.

The *human study* (Moeller and Rider) *should be retained as the basis for the chronic RfD*, with an additional safety factor imposed to compensate for a one gender study, in the face of evidence indicating the other gender to be more sensitive.

Insofar as the human study is replaced by the rat study for derivation of the chronic RfD, an additional 3X safety factor should be imposed upon the existing chronic RfD in the absence of a definitive NOEL for cholinesterase inhibition and reason to believe rats may be less sensitive due to the presence of plasma carboxylesterase.

Additional testing in animal models should be required to further quantitate existing evidence of *greater sensitivity of females in terms of cholinesterase inhibition.*

Selected slides from the acute and subchronic neurotoxicity studies should be submitted for independent *pathology assessment of retinal tissues*. Also, lower dose groups in the acute study should be examined for retinal anomalies.

After much expression of differences of opinion at committee meetings, the following have now become additional testing requirements that remain to be satisfied: a) subchronic inhalation study, b) developmental neurotoxicity study, c) cholinesterase assessments of young versus adult animals in connection with the developmental neurotoxicity study, d) additional cholinesterase testing in the dog. The *incomplete status of the data base* as evidenced by these outstanding studies, further supports retention of the FQPA 10X factor for the protection of infants and children as *required by Congress.*

B) Concerning the External Peer Review of Non-Cancer Issues

EPA's External Peer Review mechanism was pursued as a method of resolution of differing opinions between myself and the committee. After much consideration of the Panelists' comments, as explained in various memoranda, I am convinced the weight of opinion of these experts serve to support the findings expressed above (excepting additional testing in the dog). People are encouraged to examine the documents now available on the internet.

III) ***Additional Expressions of Concern***

A) In 1991, the California Department of Health published their "Health Risk Assessment of Aerial Application of Malathion Bait" Among many findings in this publication was that certain of the higher exposure population groups were receiving sufficient exposures to exceed the REL for cholinesterase inhibition. By contrast, the more recent EPA exposure assessments evidently do not confirm this finding. In my view, the two approaches should be compared side by side for correctness.

B) When malathion is being applied in such manner that people are exposed, or at least who claim they are being exposed and experience symptoms, on-site analytical data, such as that which might be obtained by an industrial hygenist, that could address the question of whether there is meaningful exposure to various chemical entities with quantitation of the same, is usually not obtained. Without such data obtained on a frequent basis, during actual application, reason may not prevail in such settings. I therefore recommend regular on-site analysis which could help secure enforcement of proper application, and also alleviate public anxieties through improved

risk communication.

Brian Dementi, Ph.D., D.A.B.T.
Senior Toxicologist
Toxicology Branch/HED